Available Online at www.jddt.in

ISSN: 2320 - 4230

Journal of Drug Discovery and Therapeutics 2 (22) 2014, 63-66

RESEARCH ARTICLE

A prospective study of toxicity profile of Cisplatin – Etoposide combination chemotherapy in Advanced Non Small Cell Lung Cancer

Shiddalingesh Salimath [*1], Mahadevappa Gudi [2], Reneega Gangadhar [3]

Department of Pharmacology, Karnataka Institute of Medical Sciences, Hubli, Karnataka, India.[1]

Department of Anaesthesiology and Critical Care, Akash Institute of Medical Sciences, Bangalore, India.[2]

Department of Pharmacology, Government Medical College, Trivandrum, India.[3]

Received 17 October 2014; Accepted 22 October 2014

ABSTRACT

Platinum based combination doublet chemotherapy is an accepted standard of care for advanced NSCLC. Presently Cisplatin-Etoposide combination chemotherapy is most commonly used regimen for advanced NSCLC and the data regarding the toxicity profile of this regimen is scarce in south Indian population.

AIMS: To study the different types of toxicities seen in patients on Cisplatin–Etoposide regimen, to assess the severity of toxicity by grading them according to the WORLD HEALTH ORGANISATION (WHO) toxicity grading.

PATIENTS AND METHODS: Fifty patients with chemotherapy-naive advanced NSCLC were enrolled between February 2008 and December 2009. Additional criteria included karnofsky performance status ≥60, and adequate organ function. Patients received Cisplatin 80 mg/m^2 iv on days 1 and 2 with Etoposide 100mg/ m^2 on days 1to 3 of consecutive 21 days cycle. Such 6 cycles were given.

RESULTS: Haematological toxicities of grade 3 or 4 included leukopenia (52%) and anemia(2%). Non-hematological toxicities OF GRADE 2 included Nausea (68%), Vomiting (12%), and alopecia (100%).

CONCLUSION: The most prevalent toxicities observed were leukopenia, nausea, vomiting and alopecia

Key words: Cisplatin – Etoposide, Carcinoma, Non-Small-Cell Lung, Toxicity

INTRODUCTION:

Lung cancer is the most common cause of cancer related death for both men and women, responsible for 1.3 million deaths annually.[1,2.] Lung cancer is also the most common cancer in the world and every year 1.35 million new cases are diagnosed.[3] Lung cancers are classified into two main categories: small-cell lung cancers (SCLC), which account for about 20% of cases, and non-small-cell lung cancers (NSCLC), which account for the other 80%.

Treatment for NSCLC is based on the clinical stage of the disease, as denoted by the tumour-node-metastasis (TNM) staging system, which is used internationally.[4] Patients with early stage 1 or 2 disease undergo potentially curative surgical resection. However majority of patients with NSCLC usually present at an advanced stage (111b/4) when a more beneficial form of therapy like surgery/radiotherapy cannot be offered. These patients have median survival time of less than a year and very few survive beyond five years.

Systemic chemotherapy is the accepted standard of care for advanced NSCLC. Many studies conducted in the past two decades have demonstrated that platinum based doublets regimen provide modest survival advantage. The superiority of a two-drug combination over a single agent was demonstrated by the Cancer and Leukemia Group B (CALGB) 9730 trial ,[5] and further confirmed in a meta-analysis performed by Delblado et al in 2004.[6] Taken together, these results led to platinum based combination doublet chemotherapy becoming an accepted standard of care for stage IV disease.

There are many platinum based chemotherapy regimens available for the treatment of advanced NSCLC. The most popular is the Cisplatin – Etoposide regimen in our institute. Data regarding use of Cisplatin – Etoposide regimen is very sparse especially in the Indian population. We have therefore conducted a prospective study of toxicity profile of cisplatin – etoposide combination chemotherapy in advanced NSCLC. Our objective was to study the different types of toxicities seen in patients on Cisplatin–Etoposide regimen, to assess the severity of toxicity by grading them according to the WHO toxicity criteria and Karnofsky performance status

*Corresponding author: Dr. Shiddalingesh Salimath || E-mail: sid.kims@gmail.com

MATERIALS AND METHODS:

This was a Prospective observational study in the Department of Radiotherapy, Government Medical college, Thiruvananthapuram. Patients with histologically or cytologically confirmed stage IIIB/IV NSCLC who were > 20 years at the time of diagnosis and had not previously received chemotherapy were recruited for the study. Patients were also required to have a karnofsky performance status ≥60.Those receiving another chemotherapy regimen, those with inadequate hematopoetic, hepatic and renal function, and pregnant ladies were excluded from the study. The study was approved by the institutional research board and human ethics committee. Patients were required to provide written informed consent prior to entering the study. The patients were subjected to a complete blood cell count, a differential count, routine chemistry measurements, chest radiography before treatment onset.

TREATMENT SCHEDULE:

Patients received six cycles of Cisplatin 80 mg/m^2 iv on days 1 and 2 with Etoposide 100mg/ m^2 iv on days 1 to 3 of consecutive 21 days cycle. Antiemetic (Granisetron) was also given before starting chemotherapy**.**

Patients were administered the scheduled chemotherapy and were observed for the occurrence of immediate toxicities. The patients were followed up during repeat visits and were assessed to detect the development of any toxicity during the course of chemotherapy and review visits on the 10^{th} day. All the toxicities that have occurred were recorded in the proforma sheet and graded according to the WHO guidelines.

Data analysis was done with the help of Excel 2007. The toxicity grades were entered in the Excel 2007 worksheet for each variable. The highest toxicity during any cycle was considered as the toxicity grade for that patient. Performance status was assessed using Karnofsky performance status scale.

WHO grades toxicities into 4 grades (grade 0 to grade 4) are ascending grades of the toxicity. Grade 0 represented absence of the toxicity and grade 4 is the maximum toxicity that can occur for a variable except alopecia where grade 2 is the highest toxicity (complete hair loss)

RESULTS:

A total of 50 patients of histologically proven advanced Non Small Cell Lung Cancer, were studied. All the patients recruited for the study were males with Karnofsky performance status ≥60. The age range of patients (table 1) included in the study were between 45 and 70 with a mean age of 57 years. The maximum number of patients was in the age group of 56-65 years

Table 1: Age wise distribution of patients

Age Group	Cisplatin + Etoposide; n=50
35-45	2 (4%)
46-55	13 (26%)
56-65	33 (66%)
>66	2(4%)

Table 2: Treatment related toxicities (graded according to WHO toxicity grading)

	Grade 1	Grade 2	Grade 3	Grade 4	aggregate toxicity
Toxicity					
Anemia	2 (4%)	2 (4%)	0	0	4(8%)
Leucopenia	8 (16%)	8 (16%)	26 (52%)	0	42(84%)
Thrombocytopenia	2 (4%)	2 (4%)	0	0	4(8%)
Nausea	13 (26%)	34 (68%)	1 (2%)	0	48(96%)
Vomiting	32 (64%)	6 (12%)	0	0	38(76%)
Stomatitis	2 (4%)	0	0	0	2(4%)
Diarrhea	4 (6%)	0	0	0	4(8%)
Alopecia	0	50 (100%)	0	0	50(100%)
Myalgia	6 (12%)	0	0	0	6(12%)
Arthralgia	3(6%)	0	0	0	3(6%)
Per. Neuropathy	3(6%)	0	0	0	3(6%)

The most common toxicities encountered were Leucopenia (84%), Nausea (96%), Vomiting (76%), and alopecia (100%) as listed in table 2.

Among Hematologic toxicities, leucopenia developed in 42 out of 50 patients enrolled for the study. A Majority of patients experienced grade 4 leucopenia. Furthermore only 4 patients developed Anemia and Thrombocytopenia.

Nausea and Vomiting were most distressing symptomatic toxicities. Grade 2 nausea developed in 68% of the patients whereas grade 2 vomiting was seen only in 12% of the patients. All patients in the study developed complete alopecia during the course of chemotherapy.

The occurrence of other side effects was less common. Only 2 patients developed stomatitis, 4 patients developed grade 1 diarrhea. Myalgia of grade 1 was experienced by six patients. Arthralgia and neuropathy developed in 3 patients each.

DISCUSSION:

The side effects of anticancer therapy are well known and limit the effectiveness of therapy prompting investigators to continue seeking new therapies or combinations that can produce a high response while reducing the incidence and severity of side effects.

This study was undertaken to understand the toxicity profile Cisplatin - Etoposide regimen used for chemotherapy in advanced Non Small Cell Lung Cancer. All the patients receiving Cisplatin+Etoposide developed at least one adverse event during the course of chemotherapy.

The most prevalent toxicities were hematologic in nature. Most patients in the study progressed to grade 3 leucopenia (42%). Thrombocytopenia and anemia were infrequent. C.P. Belani et al,[7] study also demonstrated higher occurrence of grade 3 and 4 leucopenia (44.9%), whereas Anemia and thrombocytopenia were less frequent. Similar observations were made by Perng RP et al[8] in Chinese patients, where 30.8% of patients developed leucopenia, while occurrence of anemia (15.4%), and thrombocytopenia (15.4%) was less common.

Different gastrointestinal adverse effects like nausea, vomiting, stomatitis and diarrhea were evaluated. The patients developed more nausea (96%) and vomiting (76%). Stomatitis and diarrhea were very infrequent. In a study done by Felipe Cardenal et al,[9] occurrence of grade 3 or 4 nausea and vomiting was as high as 26% in patients receiving Cisplatin+Etoposide regimen

All the patients on Cisplatin+Etoposide regimen developed complete hair loss. This was in contrast to lower incidence of alopecia (51%) reported by Felipe Cardenal et al.[9]

The occurrence of other side effects was less common in our study, this was consistent with findings of previous studies done by C.P. Belani et al,[7] and Felipe Cardenal et al.[9]

CONCLUSION:

This study was undertaken to assess the toxicity profile of Cisplatin Etoposide regimen in advanced non small cell lung cancer. The most prevalent toxicities observed were leukopenia, nausea, vomiting and alopecia. Most of the data obtained in the study were consistent with the data available in the literature. The small differences between this data and the Western data could be due to the ethnic differences and needs to be evaluated. A drawback of the study is the small sample size. By increasing the sample size and the duration of the study the comparison of the toxicity profile, tolerability and survival rate can be assessed with a better possible outcome. Nevertheless this study will enable proper selection of the patients for undergoing chemotherapy with Cisplatin Etoposide regimen as well as adequate implementation of countermeasures to avoid development of toxicities during the chemotherapeutic cycles.

DECLARATIONS:

Funding: None

Competing interests: None declared

REFERENCES:

1. World He alth Organization (2004). "Annex Table 2: Deaths by cause, sex and mortality stratum in WHO regions, estimates for 2002". The world health report 2004. Available at http:// www.who.int/whr/2004/ annex /topic/en/annex_2_en.pdf. Accessed 29 May 2014.
2. American Cancer Society. Cancer Facts and Figures 2009. Atlanta: American Cancer Society; 2009. Available at http://www.cancer.org/Research/Cancer Facts Figures/Current Cancer Facts Figures /500809 web - pdf. Accessed 29 May 2014.
3. Ferlay J. Cancer Incidence, Mortality and Prevalence Worldwide. Ann Oncol 2005; 16(3):481-88.
4. Mountain CF. Revisions in the international system for staging lung cancer. Chest 1997;111: 1710-17.
5. Lilenbaum RC, Herndon J, List M. Single-agent (SA) versus combination chemotherapy (CC) in advanced non-small cell lung cancer (NSCLC): a CALGB randomized trial of efficacy, quality of life (QOL), and cost-effectiveness. Proc Am Soc Clin Oncol 2002; 21: 1-2.

6. Delbaldo C, Michiels S, Syz N. Benefits of adding a drug to a single-agent or a 2-agent chemotherapy regimen in advanced non-small cell lung cancer. JAMA 2004; 292: 470–84.

7. C. P. Belani, J. S. Lee, M. A. Socinski. Randomized phase III trial comparing cisplatin–etoposide to carboplatin–paclitaxel in advanced or metastatic non-small cell lung cancer. Ann Oncol 2005; 16: 1069–75.

8. Perng, YM Chen, J Ming-Liu. Gemcitabine versus the combination of cisplatin and etoposide in patients with inoperable non-small-cell lung cancer in a phase II randomized study. J Clin Oncol 1997; 15: 2097-102.

9. Felipe Cardenal, M. Paz Lo´pez-Cabrerizo, Antonio Anto´n. Randomized Phase III Study of Gemcitabine-Cisplatin versus Etoposide-Cisplatin in the Treatment of Locally Advanced or Metastatic Non–Small-Cell Lung Cancer. J Clin Oncol 1999;17:12-18.

